Journey of Versican in Multiple Myeloma: From Diagnosis to Therapeutics

Nidhi Gupta*
Dept. of Biochemistry, All India Institute of Medical Sciences, New Delhi, India
Email: 1992nidhigupta@gmail.com

The term "cancer" was not very much familiar few decades back but nowadays it is being known by the general public. The people got scared by listening this word and the patient after knowing that he is suffering from cancer would loses hope for life.

What is cancer??? What is the reason for frequent conversation of this term???

Cancer is the proliferation of abnormal cells in the body which replaces normal healthy cells and disturbs the homeostasis of the biological system.

The first and foremost reason for this awareness about cancer is the day by day increasing incidence of cancer in the world including India where cancer is one of the leading causes of death among adults. Recently, the Indian Council of Medical Research proposed that by 2020, India might register over 17 lakh new cases of cancer and over 8 lakh deaths associated with it. Research is being carried out on cancer from the past many decades but still there are various things yet to explore. The exact phenomenon of its occurrence is not known but it has been observed that the changes in lifestyle, environmental deterioration and mutations in the genome contribute to the increasing cancer incidence. Cancer ranges from solid tumors (includes cancer in an organ like cervical, bladder, renal cancer, etc.) to blood cancers (or hematological malignancies such as leukemia, myeloma, lymphoma, etc.).

The deaths due to cancer are on rise either because of delayed diagnosis or inappropriate treatment. With the advent of science and technology, numerous therapies have been emerged which have undoubtedly increase the lifespan of the cancer patients but at the same time, these are

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* Ms. Nidhi Gupta, Ph.D. Scholar from All India Institute of Medical Sciences, Delhi, is pursuing her research on "Exploring the role of Versican and its Regulation by Mirna in Multiple Myeloma." Her popular science story entitled "Journey of Versican in Multiple Myeloma: From Diagnosis to Therapeutics" has been selected for AWSAR Award.

not effective enough to completely abolish this disease from the biological system. Hence, most of the cancer patients relapse which arises many questions yet to answer. One such deadly blood cancer is Multiple Myeloma (MM) in which abnormal plasma cells proliferate and accumulate in the bone marrow. This is the second most common hematological malignancies after Non-Hodgkin Lymphoma and accounts for 2% of all cancers & 13% of all hematological malignancies. MM with high relapse rate despite the presence of various sophisticated therapeutic approaches demands some highly effective treatment for the better prognosis of the disease.

With this objective in mind, we initiated to identify some targets having involvement in Multiple Myeloma. The way we are surrounded by various people in our day to day life without whom our life is in vain, similarly, every cancer including MM requires the surrounding tumor microenvironment or niche for their growth and development, hence, we aim to target bone marrow microenvironment in MM. This microenvironment comprises of various proteins, proteoglycans, growth factors and cytokines and we focused on proteoglycans. As per the published literature, out of various proteoglycans, chondroitin sulfate proteoglycans are found in the majority in extracellular matrix and one such chondroitin sulfate proteoglycan is "Versican" (VCAN) which have been reported to have crucial role in several solid tumors but no reports were available for VCAN in MM when we started working on this.

As there were no studies available, we firstly studied the expression of VCAN and molecules associated with it in MM patients. The expression of VCAN and its associated molecules were found to be higher in bone marrow and blood of MM patients in comparison to controls in both circulation and at molecular level. To examine whether this upregulation has some role in identification of MM or not, its diagnostic potential has been calculated and we found that VCAN showed 100% sensitivity and specificity in serum for diagnosis of MM and we have published this finding in *Clinica Chimica Acta* journal.

The increase in the levels of anything does not reflect its importance in any disease, hence, we moved a step further to investigate whether increase in levels of VCAN is limited to diagnosis of MM or it has some involvement with development and progression of the disease. To explore this hypothesis, we performed certain experiments with MM patients sample and cell lines which represent the cancerous myeloma cells in laboratory. As known by the reports, VCAN is produced in the surrounding microenvironment by the cells present in the stroma. We therefore isolated bone marrow stromal cells from the bone marrow by primary culture followed by their characterization. The expression of VCAN was determined in these stromal cells and found to be significantly higher in comparison to controls. These stromal cells secrete VCAN in the microenvironment to act on tumor cells, hence, conditioned medium (culture supernatant having VCAN) of these bone marrow stromal cells was collected and complemented in the culture medium of MM cell lines. Keeping the fact in mind that conditioned medium would consists of various components including VCAN, we supplemented VCAN antibody with conditioned medium to inhibit VCAN for comparison with the effects caused by conditioned medium alone.

The conditioned medium of bone marrow stromal cells enhanced cancer properties such as proliferation, angiogenesis and reduced apoptosis in myeloma cells which got neutralized by

supplementing VCAN antibody which shows the potential of VCAN not only as a diagnostic marker but also as a therapeutic target. Further, we identified the signaling pathways adopted by VCAN and we found that FAK and STAT downstream signaling pathways are activated by VCAN.

Subsequently, after identifying the tumorigenic potential of VCAN and discussed it as one of the important targets in MM, the question arises for its regulation to inhibit VCAN. To fulfill this objective, we first scrutinize certain non-coding RNAs, i.e., microRNAs from the target scan and literature search and found some regulating microRNAs for VCAN. We first determined their expression in MM patients and found these microRNAs at lower level in MM. Moreover, microRNAs were negatively correlated with levels of VCAN in MM proposing that upregulation of VCAN might be due to decrease in levels of microRNAs but this needs further validation.

In order to validate this fact, we used microRNA mimics and added into the primary bone marrow stromal cells and observed that levels of VCAN decrease upon transfection. Moreover, the effects caused by conditioned medium in myeloma cells were also neutralized by the action of microRNA mimics. The proliferation and angiogenesis decrease and apoptotic markers increase followed by the decrease in the downstream signaling pathways activated by VCAN.

Taken together, it could be stated that VCAN is an important molecule as far as its diagnostic and therapeutic potential is concerned in MM and it could be regulated by microRNAs. But this should be kept in mind that human body being very complex employs numerous molecules and proteins and effect of this strategy on biological system might be different. Hence, this work needs further validation in myeloma xenograft mice model in vivo which will be carried out in future and if results were optimum, clinical trials could also be performed by employing microRNA therapy. Furthermore, microRNA therapy could also be tried in combination with standard chemotherapeutic drugs which might substantiate the effect of current regimen and would be highly effective for the treatment of MM in clinical settings in future. Every research should be a successful one if it could be translated from bench to bedside. This piece of work is indeed the first key in this direction which opens up a new window for another success to employ an effective therapeutics for the treatment of Multiple Myeloma.

The work discussed in the article is my doctoral work performed under the supervision of Prof. Alpana Sharma at Dept. of Biochemistry, AIIMS, New Delhi. This article is original and has not been published elsewhere.